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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,728	03/03/2000	Bruce D. Weintraub	UOFMD.002C1	6702

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EXAMINER

LAZAR WESLEY, ELIANE M

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 12/05/2001

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
09/519,728

Applicant(s)  
Weintraub

Examiner  
Eliane Lazar-Wesley

Art Unit  
1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Sep 19, 2001
- 2a) ☐ This action is FINAL.
- 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-66 is/are pending in the application.
- 4a) Of the above, claim(s) 1-25, 32-38, 40-57, 59, 60, and 65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-31, 39, 58, 61-64, and 66 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some\* c) ☐ None of:

- ☐ Certified copies of the priority documents have been received.
- ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_
- ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5,6
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

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### **DETAILED ACTION**

1. Applicant's election without traverse of Group III in Paper No. 8 filed September 19, 2001 is acknowledged.

Claims 26-31, 39, 58, 61-64 and 66 are under consideration.

2. If applicant desires priority under 35 U.S.C. 119 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. It is noted that, in the continuing data in the first paragraph of the specification, the filing date of the provisional application does not match the date in the oath.

#### ***Claim Objections***

3. Claims 63, 64 and 66 are objected to as dependent on non-elected claims.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26, 31, 39, 58, 61, 63, 64 and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TSH heterodimers with mutations in specific regions of the alpha and beta subunit having greater bioactivity than the wild type TSH heterodimer, does not reasonably provide enablement for any TSH mutant. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 26, 31, 39, 58, 61, 63, 64 and 66 are to TSH heterodimer mutants having a bioactivity greater than the wild type TSH heterodimer.

Applicants disclose mutations in specific areas of the alpha and beta subunit of TSH, like in the  $\beta$  hairpin L1 loop at position 11-20 of the alpha subunit, and in the  $\beta$  hairpin L3 loop at position 58-69 of the beta subunit, that confer such activity to the heterodimer. However, in view of the state of the art, it is unpredictable which TSH  $\beta$  mutant, which TSH  $\alpha$  mutant, and which combination thereof, would allow for a TSH heterodimer having greater bioactivity than the wild type TSH, and it would constitute undue experiment to make and use the invention commensurate in scope with the claims.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 27-30, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grossmann, J.Biol.Chem. 272(34):21312-21316, August 22, 1997, cited by Applicants, in view of Szkudlinski, Current Opinion in Endocrinology and Diabetes, 4:354-363, 1997.

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Grossmann et al. teach genetic fusion of the TSH- $\alpha$  and  $\beta$  subunit using the carboxyl-terminal peptide of hCG  $\beta$  subunits as a linker, creating hTSH whose receptor binding and bioactivity were comparable to native TSH. These TSH have higher thermostability, and their plasma half-life is prolonged (see abstract).

They do not teach mutants with other bioactivities higher than the wild type TSH heterodimer.

Szkudlinski teaches, at page 359, second column, superagonists that have mutations in the  $\alpha$  subunit and in the  $\beta$  subunit, such that the receptor binding is 500 fold higher, and the potency is 100 fold higher compared to the bioactivity of the wild type hormone.

It would have been obvious for one of skill in the art at the time of the invention, to modify the construct of Grossmann, already known as having higher half-life and thermostability than the wild type, by mutating regions of the  $\alpha$  and  $\beta$  subunit taught by Szkudlinski as providing higher bioactivity, to create a mutant TSH with high stability and high bioactivity. One would have been motivated to do so, for therapeutic purposes like treatment of hypothyroidism.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Szkudlinski, Nature Biotechnology 14:1257-1263, 14 October 1996, teaches how to engineer superactive analogues of human glycoprotein hormones.

Szkudlinski, TEM 7(8):277-286, 1996, teaches specific areas of mutations that increase hormonal binding affinity (page 283, 3rd column).

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8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eliane Lazar-Wesley, PhD, whose telephone number is (703) 305 4059. The examiner can normally be reached on Monday-Friday from 9:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.


Official papers filed by fax should be directed to (703) 308 4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ELW

November 30, 2001

*rw*



**LORRAINE SPECTOR  
PRIMARY EXAMINER**